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Diaphragmatic Defects, Limb Deficiencies, and Ossification Defects of the Skull: A Distinctive Malformation Syndrome

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We report on prenatal and postnatal findings in 4 consecutive fetuses with a pattern of severe congenital anomalies who were born to a healthy nonconsanguineous couple. The spectrum of malformations includes diaphragmatic defects, hypoplastic lungs, omphalocele, limb deficiencies, syndactyly of toes, and ossification defects of the skull. This specific spectrum of anomalies is not fully compatible with that of any established syndrome. No prenatal exposure to any possible teratogen was found. Family history is suggestive for autosomal recessive inheritance, even though germline mosaicism in one of the parents cannot completely be excluded. © 1996 Wiley-Liss, Inc.

KEY WORDS: ossification defects of skull, diaphragmatic hernia, limb deficiencies

INTRODUCTION

Diaphragmatic hernia occurs with an incidence of 0.033–0.05% in newborn infants, but is probably higher among nonviable fetuses, even though figures will only be available after consistent registration of prenatal cases at different gestational ages. Congenital diaphragmatic defects can be both sporadic or familial and are a component of several syndromic conditions [Jones, 1988]. In 50–57% of cases, associated malformations were described, apart from lung hypoplasia and gut malrotation, which are implied in the diaphragmatic deficiency sequence [David and Illingworth, 1976]. Only few syndromes with associated limb defects are reported, including Fryns syndrome, which presents with acral defects [Fryns et al., 1979], and a spectrum of ulnar, tibial, and cardiac malformations [Holzgreve et al., 1984]. We here report on a family with 4 fetuses displaying a specific spectrum of congenital anomalies including diaphragmatic defects and severe limb deficiencies.

Prenatal ultrasonography offers the potential of early identification of severe congenital anomalies. An increasing number of syndromes and birth defects is attributable to specific defects in the genome, which might permit an even earlier diagnosis in some cases [Wilson, 1992]. However, a large number of conditions still remains, in which identification of congenital malformations and even genetic disorders primarily depend on the identification of a specific pattern of defects by sophisticated methods of ultrasonography [Wisser, 1992].

CLINICAL REPORTS

The index patient was the product of the fifth pregnancy of a 34-year-old GV PII woman and her 34-year-old husband. Both parents are healthy and nonconsanguineous. The first child to this couple is a healthy daughter. Three consecutive pregnancies (one female and 2 male fetuses) had congenital malformations detected on ultrasonography. Because of these severe malformations the parents had opted for termination of these pregnancies (Fig. 1).

II-2

This female fetus was diagnosed in the 21st gestational week by ultrasound study as having a diaphragmatic defect with protrusion of the stomach into the thoracic cavity. Termination of pregnancy had been induced after ultrasound detection of severe congenital malformations. A bilateral posterolateral diaphragmatic defect with protrusion of the stomach, bowel, spleen, and part of the liver into the thoracic cavity and severe lung hypoplasia were found on autopsy. No further congenital anomalies were found.

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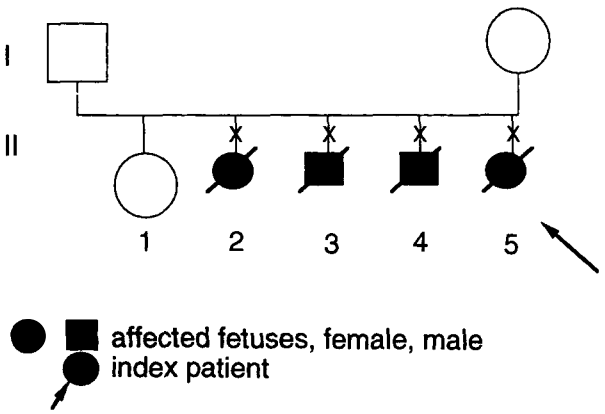

Fig. 1. Pedigree of the family with 4 affected fetuses. No parental consanguinity is known.

II-3

This male fetus was diagnosed in the 17th week of pregnancy with a posterolateral left-sided diaphragmatic defect with prolapse of stomach, bowel, spleen, and part of the left lobe of the liver into the thoracic cavity and lung hypoplasia. A small omphalocele, which contained partially calcified liver tissue, and an additional spleen were found on autopsy. The placenta was small (67.9 g; <5th centile; Fig. 2).

II-4

The third fetus, also male, had been diagnosed on ultrasound study as having a diaphragmatic defect and limb defects, herniation of the stomach into the thoracic cavity, and shift of the heart to the right. The parents again opted for termination of pregnancy, which was induced in the 23rd week of gestation. On autopsy there were a complete bilateral posterolateral diaphragmatic defect, severe lung hypoplasia, and malrotation of the gut. In addition, there were syndactylies of the 4th and 5th fingers of the right hand, malposition of the right arm, syndactyly of the 4th and 5th toes on the left foot, and only one long bone in the left leg (Fig. 3). Antecubital and axillary pterygia on the right upper limb were visible. The placenta was small (116 g; <5th centile). Chromosomes from peripheral lymphocytes in this fetus were normal, 46,XY.

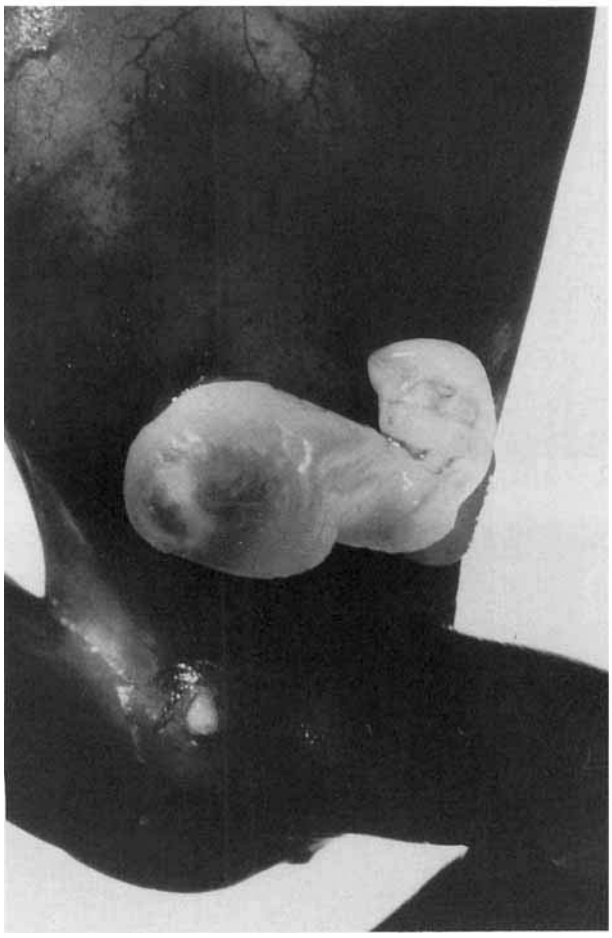

Fig. 2. Omphalocele in fetus II-3 with herniation of part of the liver.

Fig. 3. External aspect of the fetus II-4, displaying limb defects of the right upper limb and the left lower limb.

Case II-5

The course of the pregnancy with the index patient was uneventful. A first ultrasound investigation at 13 weeks of gestation was normal. A detailed ultrasound scan was requested because of the previous history of severe congenital malformations and was performed at the 17th week of gestation. It showed ossification defects of the skull, hypoplasia of the left femur and the left os ileum, dextrocardia, scoliosis, and a diaphragmatic defect (Fig. 4). Chromosomal analysis from placenta sampling and amniotic fluid showed a normal karyotype 46,XX. Because of the multiple congenital defects the parents requested termination of the pregnancy. After prostaglandin induction, spontaneous expulsion of the fetus occurred at 22 weeks of gestation.

Autopsy confirmed the sonographic findings (Fig. 2). In addition the following anomalies were found: defective ossification of the skull with fusion of the arachnoid with the subcutaneous tissue, bilateral posterolateral diaphragmatic defect, hypoplastic lung, viscerothorax with protrusion of the liver, spleen, and stomach into the thoracic cavity, shortness of the left humerus and the distal parts of radius and ulna of the left arm, syndactyly of digits 3/4, clinodactyly of the 2nd and 5th finger, axillary and antecubital pterygium on the left side, missing left os ileum and left femur, with only a single bone in the lower limb, presumably representing the tibia. The tibia was short as was the left foot, in comparison to the right side. Lower insertion of the first toe and syndactylies of the toes 2/3 and 4/5. The external genitalia were female, while there was only one gonad

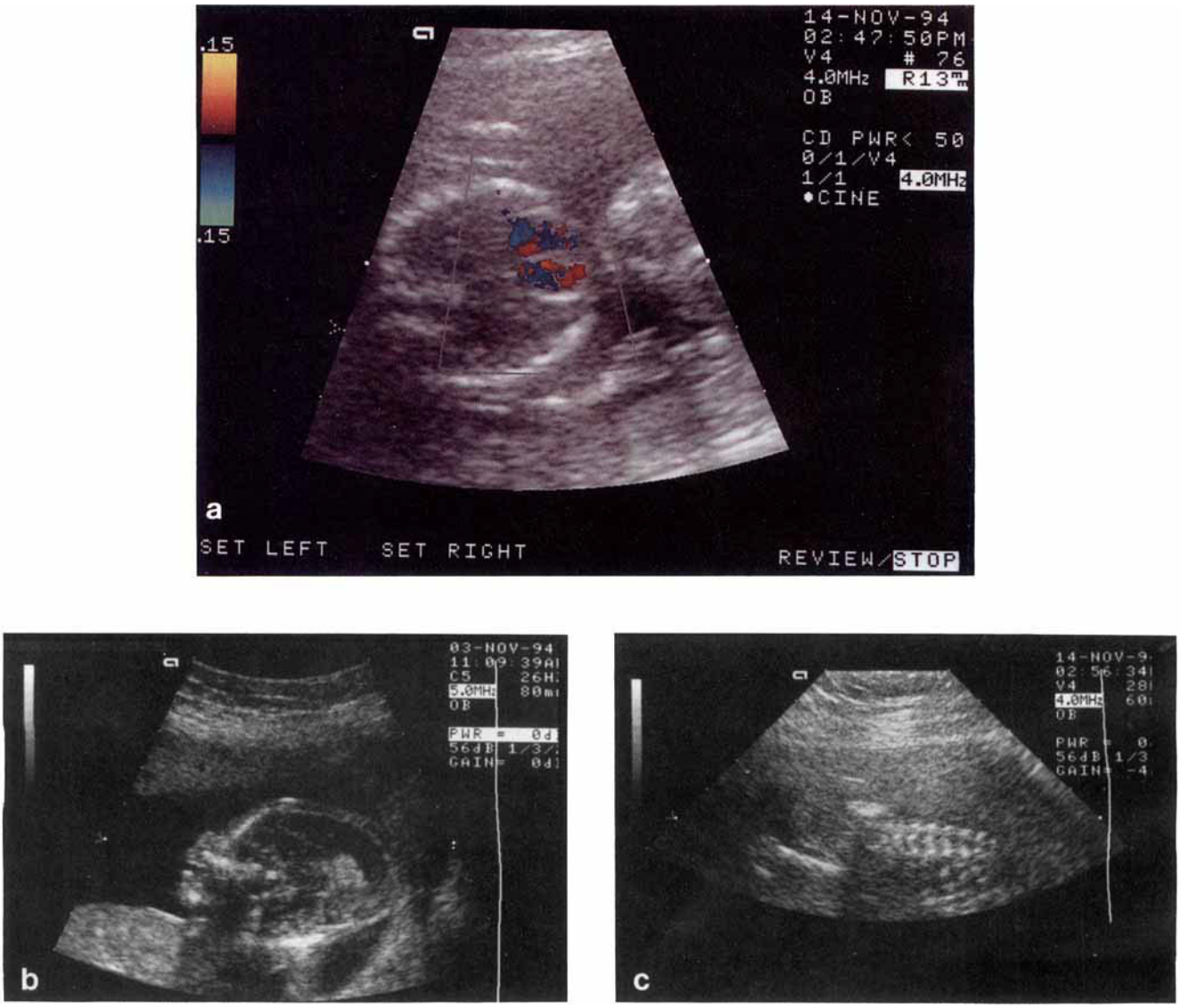

Fig. 4. Ultrasound findings of fetus II-5. **a:** Dextroposition of the heart, indicating diaphragmatic defect; **b:** abnormal skull; and **c:** hypoplasia of the left os ileum.

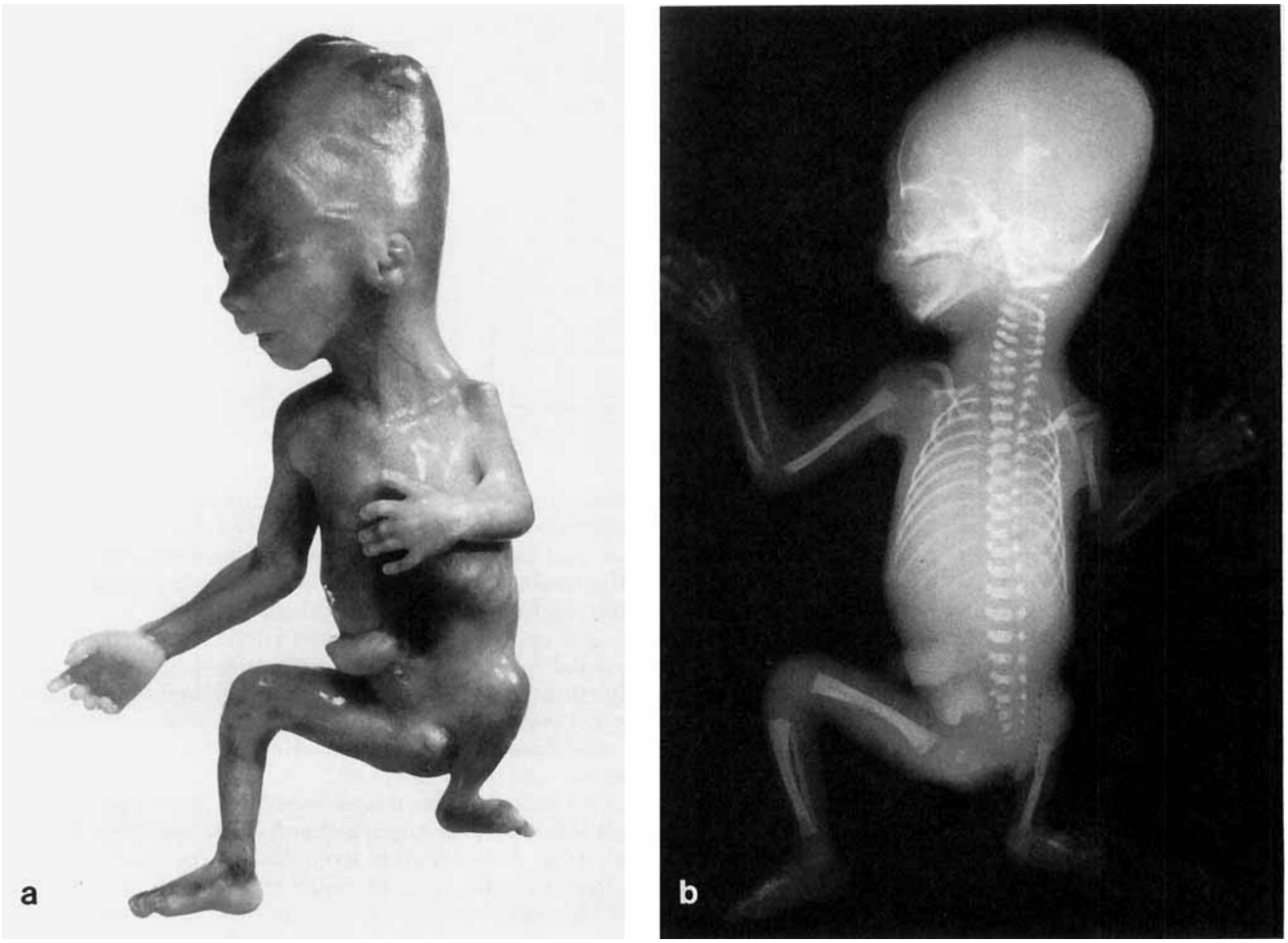

Fig. 5. **a:** Clinical aspect of the fetus II-5, showing left upper and lower limb defects with shortness of the humerus, axillary and antecubital web, abnormal pelvis, syndactyly of fingers 3/4 and toes 2/3 and 4/5. No specific facial anomalies were present. **b:** X-ray view showing small scapula and single bone in the left leg, presumably representing the tibia.

(ovary); the uterus was absent. The placenta was found to be small (85.1 g; <5th centile for gestational age).

X-ray films showed a small scapula on the left side, a short humerus and short radius and ulna; the os ileum was absent: the left leg was composited of only one bone, presumably the tibia, and of 3 metatarsals as represented on histologic study (Fig. 6).

DISCUSSION

The spectrum of additional congenital anomalies as displayed by the 4 fetuses from this family consists of diaphragmatic defects and associated limb deficiencies. There is clinical variation among the congenital malformations in these cases, with more severe limb anomalies having occurred in the last 2 fetuses. Even though autopsy reports were less informative in the first 2 pregnancies, major defects, such as severe limb deficiencies, would clearly have been reported. However, the diaphragmatic defect is constant in all 4 fetuses.

The type of defect in the fetuses from the family described here is consistent with the most frequently found diaphragmatic defect, the posterolateral (dorsolateral) type (Bochdalek). This type of diaphragmatic defect occurs mainly on the left side, but can extend to the right, as in fetuses II-2, II-4, and II-5.

Embryonic development of the diaphragm starts at the end of the 3rd gestational week and should be com-

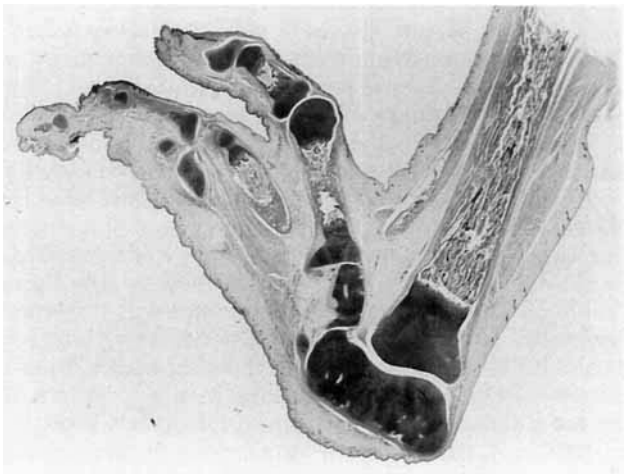

Fig. 6. Histological preparation of the left lower leg (HE stain).

TABLE I. Summary of Clinical Findings

	Findings this report				Schinzel [1990]	
Defects	II-2	II-3	II-4	II-5	Pat. 1	Pat. 2
Diaphragmatic defect	+	+	+	+	+	−
Lung hypoplasia	+	+	+	+	+	−
Malrotation of gut	−	−	+	−	−	−
Omphalocele	−	+	−	−	−	−
Abnormal truncus Pulmonalis	−	−	+	−	−	−
Limb defects	−	−	+	+	+	+
Absent uterus	−	−	−	+	−	+
Small placenta	−	+	+	+	−	−
Os ileum defect	−	−	−	+	?	+
Skull defect	−	−	−	+	?	+

pleted in the 6th gestational week [Moore, 1982]. In the third fetus hypoplastic scapula and os ileum on one side are suggestive for a very early time of disturbance of limb development, presumably during the 4th embryonic week or earlier. Thus, the time during which embryonic development of the fetuses was disrupted by either a genetic event or teratogenic agents can, with some limitations, be estimated by the pattern of anomalies, as found in these fetuses. This is also in agreement with observations from population-based studies on limb deficiencies, where diaphragmatic defects occurred in 3 of 18 liveborn cases with complete absence of the lower limbs [Froster and Baird, 1990].

The association of limb defects and diaphragmatic hernia is rare among liveborn infants. There are several syndromes which can clearly be differentiated on clinical criteria: The syndrome described by Fryns et al. [1979] has only smaller acral defects of the limbs (such as hypoplastic fingernails and distal phalanges), cloudy cornea, and holoprosencephaly. The combination of defects described by Chen et al. [1984] involves more severe congenital contractures and usually only a small diaphragmatic hernia. Gershoni-Baruch et al. [1990] reported on a single case with diaphragmatic hernia, omphalocele, and hepatic cyst with radial defects. Five sporadic cases were described by McCredie and Reid [1978], with a combination of limb deficiencies and diaphragmatic hernia. However, only the first case had a limb defect compatible with the limb deficiencies observed in the 4 fetuses described here. Schinzel [1990] reported on 2 sisters of a nonconsanguineous couple with phocomelia in both patients, while a diaphragmatic defect, genital anomalies, and skull defects had occurred in only one of them. The most distinctive feature of these 2 families is the asymmetry of limb defects in the present case and the consistency of a diaphragmatic defect in all 4 fetuses described in this report (Table I). The most compatible spectrum of congenital anomalies to our findings was described by Holzgreve et al. [1984] in a female fetus, who died within 45 minutes of birth. The malformations in this newborn included a dorsolateral type diaphragm defect, hypoplastic left heart, contralateral limb defects (with respect to the side of the diaphragmatic defect) with absence of the ulnar digits on the right, shortness of the right lower limb with inversion of the foot, and radiologically verified deficiency of the right tibia. In the fetuses described in the present report, limb defects occurred on the ipsilateral side of the diaphragmatic hernia in II-5, but also on the contralateral side in II-4.

The cause of the spectrum of defects in the cases presented here is compatible with autosomal recessive inheritance. However, germline mosaicism in one parent must also be considered. Teratogens, such as vitamin A, were described in animal studies to cause diaphragmatic defects [Wilson et al., 1953]. Thus, the possibility of an unknown teratogen taken by the mother during all of her pregnancies also needs to be considered as one possible causal factor, even though no medication or other external factors were recalled by the mother. With respect to prenatal diagnosis by ultrasonography, the ossification defects of the skull and diaphragmatic hernia were the most striking and early detectable manifestations in these fetuses. The spectrum of congenital anomalies found in this family is specific and has, to the best of our knowledge, not been previously reported. In all likelihood we would consider this to be a distinct new autosomal recessive syndrome.

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